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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/984,900	12/04/1997	ANTHONY J.F. D'APICE	06862/005002	2819

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	35

DATE MAILED: 12/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/984,900	Anthony J.F. D'Apice et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Oct 7, 2002* .

2a) This action is **FINAL**. 2b) X This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-3, 46-51, 67, and 70-77* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) X Claim(s) *1-3, 46-50, 67, and 70-73* is/are allowed.

6) X Claim(s) *51 and 74-77* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____ .
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). 32
4) Interview Summary (PTO-413) Paper No(s).
5) Notice of Informal Patent Application (PTO-152)
6) Other:

DETAILED ACTION

Applicants' amendment filed 10-7-02 has been entered. Claims 78 and 79 have been canceled. Claims 1-3 and 67 have been amended. Claims 1-3, 46-51, 67 and 70-77 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 51 and 74-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell transformed with a nucleic acid molecule comprising SEQ ID No. 7 *in vitro* or a method for generating a porcine cell having an inactivated alpha 1, 3 galactosyltransferase (GT) gene *in vitro*, wherein prior to disruption said gene encodes a porcine α-1-3 GT with amino acid sequence of SEQ ID No. 10, does not reasonably provide enablement for a method for generating a porcine cell having an inactivated alpha 1, 3 galactosyltransferase (GT) gene *in vivo*, wherein prior to disruption said gene encodes a porcine α-1-3 GT with amino acid sequence of SEQ ID No. 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 51 and 74-77 read on a method for generating a porcine cell having at least one disrupted α-1-3 galactosyltransferase (GT) gene *in vitro* and *in vivo*, including a method of producing a porcine cell with disrupted α-1-3 GT gene via making a transgenic animal, such as a porcine, and a method of producing a porcine cell with disrupted α-1-3 GT gene in a subject via gene therapy *in vivo*.

The specification discloses the purification of human anti-gal antibody, inhibition of human serum-induced lysis of porcine cells by sugars, e.g. melibiose, galactose, or by depleting anti-gal antibody in the serum, characterization of porcine α-1,3 GT gene, preparation of DNA construct containing interrupted mouse α-1,3 GT gene (pNeoαGT10.8B), production of α-1,3 GT homologous knockout mice by injecting mouse ES cells transfected by pNeoαGT10.8B into blastocyst and confirm the lack of the galactose α-1,3 galactose epitope in said knockout mice by anti-gal and IB4 lectin binding assay, and the resistance of spleen cells from knockout mice to lysis by human serum.

The specification fails to provide adequate guidance and evidence for producing a transgenic animal, such as a transgenic porcine, having disrupted α-1-3 GT gene in its genome and the resulting phenotype of said transgenic animal, such as a transgenic porcine.

The state of the art in the fields of transgenic animal at the time of the invention was unpredictable, the transgene expression and physiological results of such expression is not always accurately predictable. For example, the incidence of expression of the same fusion genes is much higher in transgenic mice than in pigs, introduction of human growth hormone

transgene in mouse results in mammoth mouse phenotype, whereas introduction of same transgene into pigs results in several health problems, including lameness, lethargy, gastric ulcers, and anoestrous gilts (Palmiter et al., 1983, Science, Vol. 222, p. 809-814 (e.g. abstract); Pursel et al. 1990, J. Reprod. Fert., Suppl. Vol. 40, p. 235-245 (e.g. abstract, V)). Similarly, it is unpredictable for generating transgenic animals harboring disrupted α-1-3 GT gene. Wu et al., 1997 (Methods in Gene Biotechnology, CRC Press, Boca Raton, p. 339-365) pointed out that the approach of using ES cells carrying a single-copy mutation of a specific gene to generate knockout transgenic animal is time-consuming and costly to obtain homozygous or double-knockout mice, and another major concern is the potentially lethal effect of the targeted gene. In some cases, gene knockout results in early death of embryos and young animals, or morphologically and functionally abnormal offsprings such as blind and/or handicapped animals. Further, Sigmund, June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype" (abstract). In view of the inherent unpredictability of the phenotype of a transgenic animal, such as transgenic porcine, and the lack of availability of embryonic stem cells for species other than mouse, it would require one skilled in the art at the time of the invention undue experimentation to generate a transgenic animal, such as a transgenic porcine,

having a porcine cell containing a disrupted α-1-3 GT gene in its genome and a particular phenotype.

The specification also fails to provide adequate guidance and evidence for producing a porcine cell with disrupted α-1-3 GT gene in a subject via gene therapy *in vivo*.

The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA are all important factors for a successful gene therapy (e.g. bridging pages 81-82).

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art.

It should be noted that the statutory declarations as cited in the Information Disclosure Statement filed 10-4-02 have not been considered because they were not submitted. The submitted statutory declaration, Exhibit NJD-1, was not considered because it is not desirable to have it printed on an issued patent.

Conclusion

3. Claims 51 and 74-77 are rejected. Claims 1-3, 46-50, 67 and 70-73 are in condition of allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.